Right ventricular remodeling and function in pulmonary arterial hypertension

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Summary

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Pulmonary arterial hypertension (PAH) is a progressive disease of the small pulmonary arteries that results in increased pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP). As a consequence, the right ventricle (RV) has to cope with the increased afterload in order to provide sufficient cardiac output (CO). The RV develops hypertrophy, dilates and shows changes in metabolism. However, the RV is not suitable to cope with longstanding pressure overload, resulting in RV maladaptation, decreased RV function and ultimately RV failure and death. The current medical treatment strategy is aimed to improve RV function by reducing the afterload. During the last decade, multiple medical therapies have been developed that have mainly pulmonary vasodilator effects resulting in reduced PVR and improved CO. Despite these therapeutic effects, survival remains unsatisfactory. Therefore more insights are warranted in how RV dysfunction evolves structurally and functionally during the course of disease and under medical treatment.
The aims of this thesis are twofold. The first aim was to provide improved insights in RV structural remodeling to pressure overload. Secondly, we aimed to assess the changes in RV adaptation and function over time in relationship to the changes in afterload under current PAH targeted medical therapies. In this thesis, we performed RV assessment by magnetic resonance imaging (MRI), which is considered the gold standard to measure RV mass, volumes and function.

In **Chapter 2**, we studied the hypertrophic response of the RV in PAH patients in comparison to control subjects. The RV muscle mass does not only consist of the RV free wall but also includes many trabeculae: small muscle bundles that support the RV free wall. However, RV trabeculae have been generally ignored in previous literature. Therefore, by use of MRI and right heart catheterization (RHC), we studied in 50 PAH patients and 20 control subjects the hypertrophic response of both the RV free wall and trabeculae to pressure overload and assessed the changes in these RV mass compartments during one year of medical treatment. We found that the RV trabeculae showed a larger contribution to total RV mass in PAH patients (~35%) compared to controls (~25%) ($p < 0.001$). Moreover, in PAH patients the changes in mass of the RV trabeculae were stronger related to the changes in PVR and PAP after one year of medical treatment than the mass of the RV free wall. These results implicate that trabeculae are important contributors to RV adaptation to chronic pressure overload in PAH.

During chronic RV pressure overload, interventricular dyssynchrony is associated with leftward bowing of the interventricular septum (IVS) and disturbed IVS function. However, it is unknown what tissue alterations occur in the IVS and if they are comparable to the changes in the RV free wall. In **Chapter 3**, we studied in 17 PAH patients by MRI and PET the mass and glucose metabolism of the RV, IVS and left ventricle (LV). In addition, we studied in more detail whether cellular alterations of the IVS were comparable to the RV free wall in a monocrotoline pulmonary hypertension (PH) rat model. In PAH patients, we found that the changes in IVS mass and glucose metabolism were not comparable to the changes in the RV free wall (both p for difference <0.001). In addition, the cardiomyocyte cross-sectional area and capillary density remained preserved in the IVS but were impaired in the RV free wall of PH rats (both p interaction <0.001). Furthermore, we found that although fibrosis and inflammation were increased in both the IVS and the RV in PH rats, the magnitude of increase was significantly lower for the IVS (both p interaction <0.001). These results demonstrate that despite a similar pressure overload in PAH, IVS morphology and metabolism remain better preserved and do not resemble the remodeling of the RV free wall.

Despite a reduction in PVR accomplished by current medical therapies, survival of PAH patients remains grim. This might be explained by the fact that this PVR reduction does not automatically result in improved RV function. Therefore, in **Chapter 4** we studied the

relationship between the changes in PVR and changes in RV function and survival after medical treatment. A large group of PAH patients underwent MRI to measure RV ejection fraction (RVEF) as a measure of systolic RV function and RHC to measure PVR at baseline and after one year of treatment. We found that the changes in PVR were moderately related to the changes in RVEF ($R = 0.33$; $p = 0.001$). 68% of the patients showed a reduced PVR after medical treatment. In 75% of these therapeutic responders, this was associated with a stable or improved RV function and favorable survival. However, 25% of these patients showed despite a similar decrease in PVR, progressive RV dysfunction which was associated with poor survival.

Since male gender is associated with a poor survival, we assessed in **Chapter 5** whether this could be explained by a distinct vascular or RV response to medical treatment. At baseline, we observed that RVEF and PVR were comparable between males and females. Both genders showed a similar reduction in PVR after medical treatment (p for difference = 0.63). However, females showed an improved RVEF while males showed a deterioration in RVEF after medical treatment ($p < 0.001$ after correction for confounders) which was associated with a poor survival. One third of the effects of gender on survival was mediated by the differences in RVEF, which indicates that also other factors could play an important role in the gender disparity in PAH.
In **Chapter 6**, we hypothesized that a strong reduction in PVR after medical treatment will result in an guaranteed improvement of RV function and survival. In this chapter, we investigated the relationships between baseline PVR, PVR-response, changes in RV adaptation and function and survival after current PAH therapies. we demonstrated that a threshold decrease in the relative PVR change of more than 42% was feasible in a substantial number of PAH patients and was associated with an improvement in RV function, reduction of RV dilatation and long-term survival. A strong PVR decrease was related to the application of upfront combination therapies.

Even after years of a stable response to medical treatment (defined by a stable New York Heart Association (NYHA) functional class II-III and six-minute walking test), PAH patients may show an unexpected rapid clinical deterioration due to progressive RV failure, which is associated with a high mortality rate. If the RV would already demonstrate signs of progressive adverse remodeling during the initial stable clinical condition, assessment of RV remodeling parameters might predict an ultimate disease progression. In **Chapter 7**, we assessed in 22 five-year clinically stable patients with PAH whether differences in RV volumes, precede an ultimate disease progression. We compared regularly obtained RHC and MRI measures between twelve patients who remained stable during 10 year of follow-up and ten other patients who showed late disease progression leading to death or lung transplantation after a median duration of eight years. We found that RV remodeling can be progressive, even in PAH patients who are seemingly clinically stable during 5-10 years of follow-up. Moreover, we showed that an ultimate disease progression is preceded by changes in RV volumes and RVEF and not by differences in NYHA functional class, exercise capacity or hemodynamic parameters.

In **Chapter 8**, we provided an overview of advanced *in vivo* imaging of the RV by cardiac MRI and PET. We show that imaging of RV hypertrophy, shape, dilatation, wall stress, global function, contractility, dyssynchrony and IVS bowing, perfusion and metabolism have significantly contributed to a better understanding of the pathophysiological processes that contribute to the development of chronic RV failure in PAH. Furthermore, we explained that in the near future it can be expected that the importance of changes in tissue processes such as angiogenesis, apoptosis and neurohormonal factors will become more clear and ‘imageable’. In addition, recent advances in hybrid PET and MRI might allow integrated assessment of the RV in vivo and will be one of the most important future developments.